UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/896,053	07/17/97	JANSSENS S	0516.4951MR1

HM31/0930

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EXAMINER	
BECKERLEG, A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 09/30/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 08/896,053	Applicant(s) Janssens
	Examiner Anne Marie S. Beckerleg	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-20 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-20 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not identify the citizenship of each inventor. The citizenship of Kenneth D. Bloch is missing.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing vasodilation in a mammal comprising: introducing into the lungs of a mammalian patient in need of pulmonary vasodilation an aerosolized adenoviral vector comprising a wild type endothelial nitric oxide synthase gene operably linked to the CMV promoter, wherein the introduction of said gene into the lungs of said patient results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index, and a

method of treating hypoxic pulmonary hypertension in rats comprising introducing into the lungs of a rat in need of pulmonary vasodilation an aerosolized adenoviral vector comprising an endothelial nitric oxide synthase gene operably linked to the CMV promoter, wherein the introduction of said gene into the lungs of said rat results in pulmonary vasodilation that does not significantly affect systemic blood pressure or cardiac index, does not reasonably provide enablement for a method of treating any and all forms of primary or secondary hypertension in all mammals comprising introducing any nitric oxide synthase including endothelial nitric oxide synthase by any means into the lungs of a mammal, particularly a human mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification provides a working example of the instant invention wherein an adenoviral vector encoding endothelial NOS under the transcriptional control of the CMV promoter is aerosolized into the lungs of normal non-hypertensive rats resulting in expression of enzymatically active eNOS in lung tissue. Hypoxic hypertension was induced in the rats by mechanical ventilation with 10% O_2 and 90% N_2. The working example demonstrates that eNOS expressing hypoxic rats had reduced pulmonary artery pressure compared to hypoxic rats exposed to an adenovirus encoding bacterial Lac Z, while at the same time systemic blood pressure and cardiac index remained unchanged.

The specification does not provide an enabling disclosure for the use of either an inducible macrophage nitric oxide synthase (iNOS) or a constitutive neuronal nitric oxide synthase (nNOS)

in the instant invention. Macrophage derived iNOS differs significantly from the two constitutive forms of NOS in that its enzymatic activity is calcium independent. While, neuronal and endothelial NOS do share calcium and calmodulin dependence, they are significantly different in terms of size and amino acid homology (Janssens et al. (1992) J. Biol. Chem., Vol. 267 (21), page 14520, column 2, and page 14521, column 1). In addition, the specification notes that any nitric oxide synthase genes having amino acid additions or deletions compared to the sequence as published by the inventors can be used in the instant invention (specification, pages 12-14). The specification does not provide guidance as to the level of expression and the level of specific activity of iNOS, nNOS, or addition/deletion mutants of any nitric oxide synthase isoform required to produce a quantity of nitric oxide sufficient to induce vasodilation and decrease pulmonary artery pressure *in vitro* or *in vivo*. In the absence of evidence to the contrary , the skilled artisan would not consider it predictable that three distinct isoforms of an enzyme, or an enzyme encoding substantial additions or deletions compared to its wild type sequence, would have the same specific activity in generating nitric oxide, and therefore, would not have considered it predictable that iNOS, nNOS, or mutants thereof could be substituted for wild type eNOS in the instant invention.

The specification does not provide an enabling disclosure for the transduction of lung tissue *in vivo* with eNOS using any vector and promoter combination and any routes of delivery. The applicant's working example provides guidance for the use of a recombinant adenovirus encoding the gene for eNOS under the transcriptional control of the CMV promoter. The

specification does not provide guidance for the dosage and routes of delivery of non-adenoviral vectors expressing eNOS, such as DNA plasmid vectors or retroviral vectors, capable of expressing eNOS in the lung *in vivo*. Verma et al. teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and specifically identifies the "Achilles heel" of gene therapy as gene delivery (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2). In particular, Verma points out that, " [a] critical limitation of retroviral vectors is their inability to infect non-dividing cells, such as those that make up muscle, brain, lung, and liver tissue " (Verma et al. (1997) Nature, Vol. 389, page 240, column 1, paragraph 3). Verma also teaches that the choice of an appropriate enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector and that , " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1). In addition, while the specification teaches the aerosol delivery of adCMV-eNOS to the lung, it does not provide guidance as to the intramuscular, intravenous, or intraperitoneal injection of adCMV-eNOS that would result in transduced eNOS expressing lung tissue. Thus, based on the unpredictable effects of gene delivery using viral vectors as taught by the art at the time of filing, and the lack of guidance provided by the specification for the use of any and all vectors-promoter combinations and routes of *in vivo* vector delivery, it would have required undue experimentation for the skilled artisan to practice the instant invention as claimed.

The specification does not provide an enabling disclosure for the administration of a pharmaceutical composition comprising adCMV-eNOS and an immunosuppressive agent or a phosphodiesterase inhibitor. A pharmaceutical composition by definition must produce some beneficial effect in the host animal. Recombinant adenoviruses stimulate a strong immune response in a mammalian host resulting in the generation of anti-viral antibodies and adenovirus specific cytotoxic effector cells. The specification discloses that immunosuppressive agents such as cyclosporin or steroids can be administered simultaneously with the recombinant virus encoding NOS in order to attenuate viral clearance by the host's immune system. In fact, the art at the time of filing reveals that cyclosporin A, while a potent immunosuppressor, induces hypertension in both animals and humans. Roullet et al. further disclose that nitric oxide does not counter the effect of cyclosporin A on mesenteric artery resistance vessels in a rat model of hypertension and suggests that, " the NO generating system is impaired by Cys A"(Roullet et al. (1994) J. Clin. Invest., Vol. 93 (5), page 2244, abstract, and page 2249, column 1, paragraph 3). Therefore, in the absence of evidence to the contrary, the skilled artisan would not have considered a composition comprising two molecules which produce diametrically opposed effects in a mammal to have any pharmaceutical value. In addition, the specification does not provide guidance as to the dosage, or route of delivery of a pharmaceutical composition which combines steroids, other immunosuppressive agents, or phosphodiesterase inhibitors, and adCMV-eNOS, or any other nucleic acid encoding a nitric oxide synthase, which would generate a beneficial effect on a host. Thus, based on the art at the time of filing, and the lack of guidance provided by the

specification, the skilled artisan would not have had a reasonable expectation of success in making and using the pharmaceutical composition as claimed.

The specification does not provide an enabling disclosure for the treatment of any and all forms of primary or secondary pulmonary hypertension in all mammals including humans. The specification defines treatment as including prophylaxis, amelioration, or cure (specification, page 10, lines 10-13). Primary pulmonary hypertension is a rare and difficult to diagnose disorder. According to Giuseppe Pietra, plexogenic pulmonary arteriopathy (PPA), characterized variably by concentric laminar intimal fibrosis, plexiform lesions, and necrotizing arteritis, is the most common form of arteriopathy in primary pulmonary hypertension (Pietra (1994) Chest, Vol. 105 (2 supp.), page 3S-4S). Secondary pulmonary hypertension, on the other hand, occurs as a result of an underlying defect or condition such as cardiac septal defects, and cirrhosis. However, neointimal formation as a result of smooth muscle cell migration and proliferation resulting in a physical narrowing of the artery is characteristic of most forms of pulmonary hypertension, both primary and secondary. The applicant's working example demonstrates the treatment of mechanically induced hypoxia using AdCMV-eNOS. D. Heath, however, specifically identifies the rat as a poor animal model for pulmonary hypertension, particularly human hypertension, since, " the limited or free migration of vascular free muscle cells in human hypertensive pulmonary disease is not seen in the rat" (Heath (1993) Eur. Respir. Rev., Vol. 3 (16), page 555, abstract, and page 557, paragraph 6). Furthermore, Heath states in regards to treatment of pulmonary hypertension with vasodilators that, " [w]hile they are likely to reverse any vasoconstrictive

component, it is difficult to conceive what effect they might have on structural changes in the intima..", and that, " [p]ulmonary vasodilators are unlikely to be effective once migration of vascular smooth muscle cells has occurred" (Heath (1993) Eur. Respir. Rev., Vol. 3 (16), page 555, abstract, and page 557, paragraph 7). Thus, the skilled artisan at the time of filing would not have had a reasonable expectation of success in curing primary or secondary hypertension involving vascular smooth muscle hyperplasia using eNOS which produces the vasodilator nitric oxide. As to the prophylactic use of eNOS to prevent the development of pulmonary hypertension, the specification provides no guidance as to the administration of the instant invention to patients with a cardiac septal defect or thrombotic disease wherein pulmonary hypertension is completely prevented by eNOS expression. On the successful use of gene therapy for disease, Orkin et al. reports that, "[w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol .." (Orkin et al. (1995) "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy", page 1, paragraph 3). Therefore, based on the art at the time of filing, and the lack of guidance provided by the specification for the prophylactic prevention or cure of hypertension in all mammals, the skilled artisan would not have predicted the successful treatment of either primary or secondary hypertension using the instant invention as claimed.

In summary, as a result of the undue amount experimentation required to determine the parameters affecting successful gene delivery as listed above, the state of the art at the time of

filing which considered gene therapy of diseases as unpredictable, and the breadth of the claims, the skilled artisan would not have had a reasonable expectation of practicing the scope of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 recites the limitation "said endothelial nitric oxide synthase gene" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 9 recites "The method of treating pulmonary hypertension as claimed in claim 7...". Claim 7 is a method of inducing pulmonary vasodilation. There is no antecedent basis for a method of treating pulmonary hypertension in claim 7.

Regarding claim 17, the word "means" is preceded by the word(s) " and a " in an attempt to use a "means" clause to recite a claim element as a means for performing a specified function. However, since no function is specified by the word(s) preceding "means," it is impossible to determine the equivalents of the element, as required by 35 U.S.C. 112, sixth paragraph. See *Ex parte Klumb*, 159 USPQ 694 (Bd. App. 1967).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (1996) FASEB Journal, Vol. 10(3) A303, in view of Rosenfeld et al. (1992) Cell, Vol. 68, 143-155. The applicant claims a pharmaceutical composition comprising a nucleic acid encoding a nitric oxide synthase operably linked to an expression control element and a means for transducing said nucleic acid into pulmonary tissue. Chen et al. teaches the construction of an adenoviral vector encoding bovine endothelial NOS operably linked to the CMV promoter and its use for transducing basilar artery rings *in vitro* resulting in expression of functionally active eNOS (Chen et al., abstract). Chen et al. does not teach the *in vivo* administration of an adenoviral vector to lung tissue. Rosenfeld et al., however, provides motivation for administering a recombinant adenoviral vector to lung tissue *in vivo* by teaching that adenovirus is tropic for respiratory epithelium, and that rats injected intratracheally with a pharmaceutical composition comprising a recombinant adenovirus encoding CFTR expressed CFTR in the lung epithelia. Thus, given the motivation to use a recombinant adenoviral vector to transduce lung tissue *in vivo* as taught by Rosenfeld et al., the skilled artisan at the time of filing would have considered it prima facia obvious to use the recombinant adenoviral vector encoding eNOS as taught by Chen et al. as a pharmaceutical composition useful for expressing eNOS in pulmonary tissue.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Deborah Crouch

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Dr. A.M.S. Beckerleg

September 28, 1998